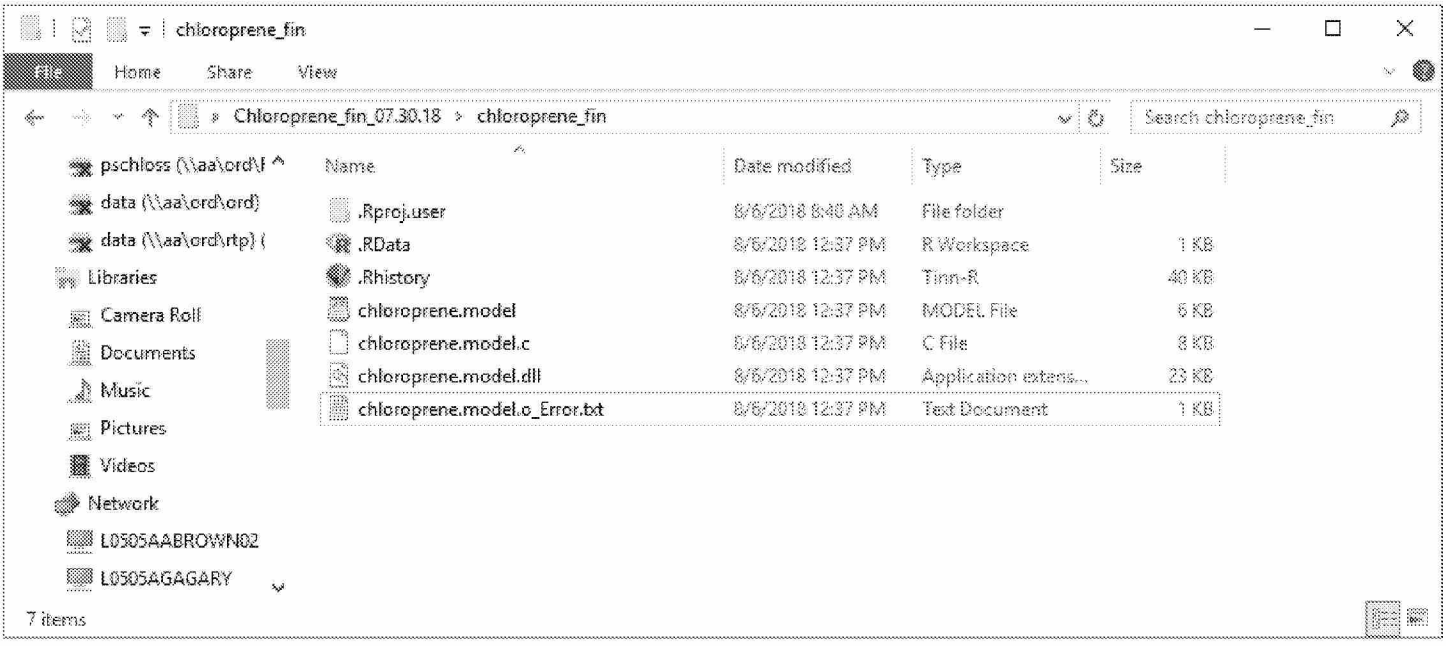
-Paul



From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Friday, August 03, 2018 2:02 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; cvanlandingham@ramboll.com; Allison Franzen <AFranzen@ramboll.com>; Jerry Campbell <JCampbell@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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Principal Consultant
1692720 - Tampa

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USA
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Message

From: Harvey Clewell [HClewell@ramboll.com]
Sent: 9/20/2018 5:13:38 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]; HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]; Jerry Campbell [JCampbell@ramboll.com]
CC: Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Robinan Gentry [rgentry@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]
Subject: RE: Chloroprene In Vitro model

Harvey Clewell
Principal Consultant

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M +1 (919) 4524279
hclewell@ramboll.com

From: Harvey Clewell
Sent: Thursday, September 20, 2018 1:13 PM
To: 'Schlosser, Paul' <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <jcampbell@ramboll.com>
Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Robinan Gentry <rgentry@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>
Subject: RE: Chloroprene In Vitro model

Hi Paul

Yes, ventilation can be a sensitive parameter in the closed chamber studies. It depends on the chemical and the concentration.

In the case of the open chamber study we performed at the Hamner, we measured the ventilation rates during the exposures. I'm attaching a draft of the manuscript I'm writing on the study so you can see the results. I can't finalize the PBPK modeling part until we come to closure on the parameters.

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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Thursday, September 20, 2018 12:44 PM
To: Harvey Clewell <HClewell@ramboll.com>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <jcampbell@ramboll.com>
Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

I had looked for those scripts, but may have over-looked them. I thought there should be legacy scripts from Matt at a minimum.

As for closed vs. open chamber, we've already established (I think you showed in your presentation here) that the model simulations of the open-chamber data are not very sensitive to the respiration rate (the SC was very low). The animals are close to steady state at the end of the exposure period, when blood concentration data are typically collected. Respiration effects how quickly you get there, but if data aren't collected during the early part of the exposure…

So the fact that one has to adjust the QP to fit closed chamber data, but not open chamber data, could also be because closed chamber data are sensitive to QP, while the data collection/study design for open chambers makes it less sensitive. Could it be that animals are also changing ventilation in open chamber studies, we just don't know it?

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Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

HI Paul

I'm pretty sure that the model and scripts for the closed chamber studies on chloroprene are included in the model documentation we sent you. I'll ask Jerry to either verify that or send them to you.

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Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

I saw the other note too, thanks.

The plots are classic for closed chamber, so my goof, but the discussion of how the exposure system might effect respiration had me thinking of nose-only. It doesn't make as much sense to me that the animals would breath differently in a closed vs open chamber.

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Sent: Thursday, September 20, 2018 8:00 AM
To: Harvey Clewell <HClewell@ramboll.com>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Paul,

Harvey is correct. 2004b is closed chamber work.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Wednesday, September 19, 2018 4:41 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Hi Paul

When you talk about the nose-only in vivo PK data from 2004, were you referring to the closed chamber studies that Marina Evans and Elaina Kenyon performed for the Himmelstein et al. 2004b publication?

Harvey Clewell
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hclewell@ramboll.com

From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Wednesday, September 19, 2018 1:39 PM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <jcampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt, all,

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As it stands, we have mostly halted our QA review, as it strongly hinges on the equilibration assumption in the in vitro modeling. The code for the in vitro and in vivo models has checked out, issues resolved, and I think all other parameter discrepancies have been resolved -- a few changes but none that should make a really large difference.

I realize it might take some time for files to be retrieved from archives and reviewed, but it's now been a couple of weeks since I provided the written details on what we are seeking. Can you tell us where things stand on your end?

The simulations I've run/provided show that the fits to the low concentration in vitro data depend significantly on the assumption that gas-liquid equilibration is not rate limiting, and the data are consistent with the possibility that it is a factor, requiring a fairly large revision in the estimated Km value(s). As is, my conclusion is that there is uncertainty due to the lack of data on the mass transfer rate, and there isn't an easy way that I can think of (or that we are likely to undertake ourselves) for estimating or bounding that uncertainty. The model results are too uncertain to use, given the data and assumptions.

If data are obtained (from archives or newly developed) that show that mass transfer is a factor, it will then be up to Denka/Ramboll to revise the in vitro parameter estimation accordingly, and propagate that into the in vivo model, before we would continue our QA.

As indicated in previous emails, our QA will also involve comparing model predictions to the nose-only in vivo PK data from 2004: the model should be able to fit with parameters adjusted in a way consistent with the hypothesis that there may be an effect of the exposure system on respiration, but this would not be exposure-concentration-dependent. That will require creating model scripts to run these simulations and compare model outputs to the data. While we are prepared to do that work as part of our QA, provided that the mass transfer data become available, we are not planning to begin that work until those data are available and any necessary revisions of the in vitro modeling have been completed. Alternately, Ramboll colleagues could create the scripts in the meantime, which would speed up the QA.

Sincerely,
-Paul

Paul M. Schlosser
NCEA, U.S. EPA
M.D. B243-01
RTP, NC 27711
T: 919-541-4130
F: 919-685-3330
E: schlosser.paul@epa.gov

From: Schlosser, Paul
Sent: Wednesday, September 05, 2018 12:06 PM
To: 'HIMMELSTEIN, MATTHEW W' <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Sorry. I was also wondering at the volume being 1.6 mL bigger than advertised, it seemed like a large discrepancy.

A memo is attached, but here is what I've gotten from looking at the code in the appendix of the report you sent:

- Data to indicate that mass transfer resistance is not significant are still lacking.

- The sample volume (VINJ) for all the CP ***oxidation*** experiments in the 2004 paper should be ~ 400 uL, including male mouse and rat liver and lung data. But the code in the report uses 385.8 uL for male data and exactly 200 uL for male data. Is the higher accuracy for the rodent male and human data supported by some measurements?

- Assuming a similar accuracy, the vial volume (VVIAL) for all experiments described in the 2004 paper should be 0.0120 L. This value should be used for male mouse and rat liver and lung data. (We'll use 0.0116 L for the female mouse and rat data and the kidney data.)

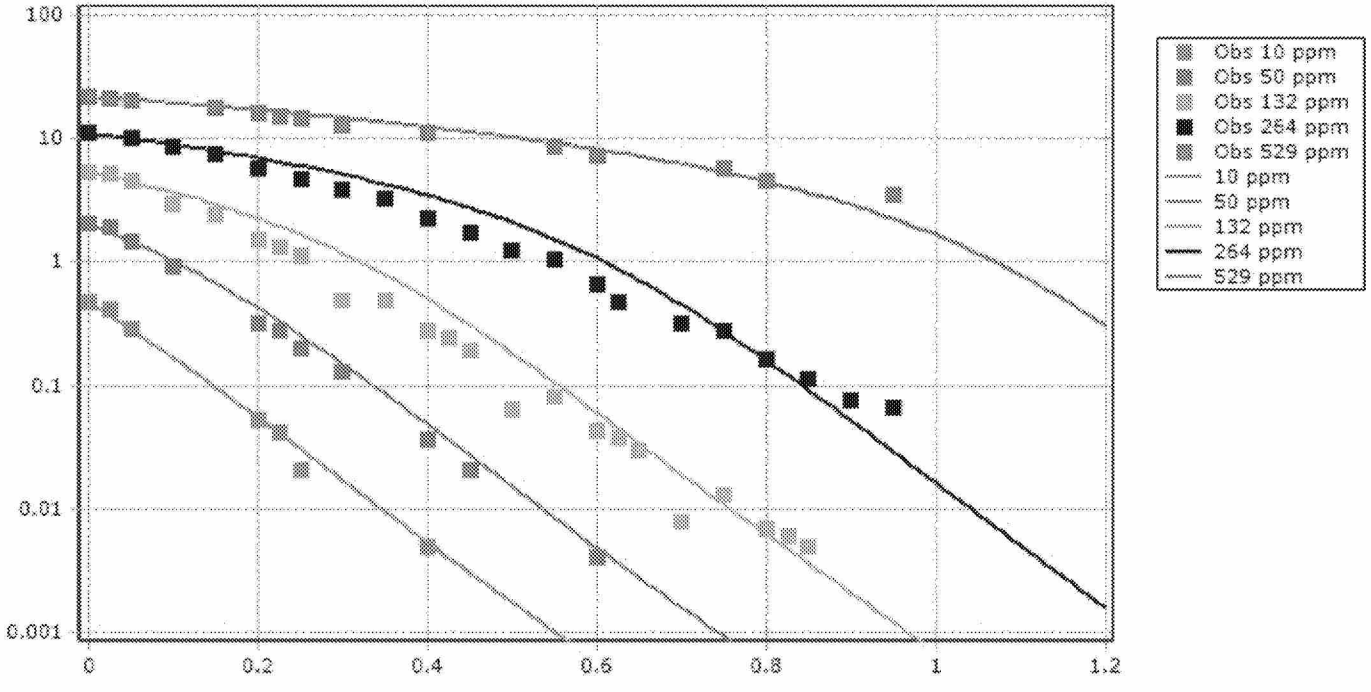
Thanks,
-Paul

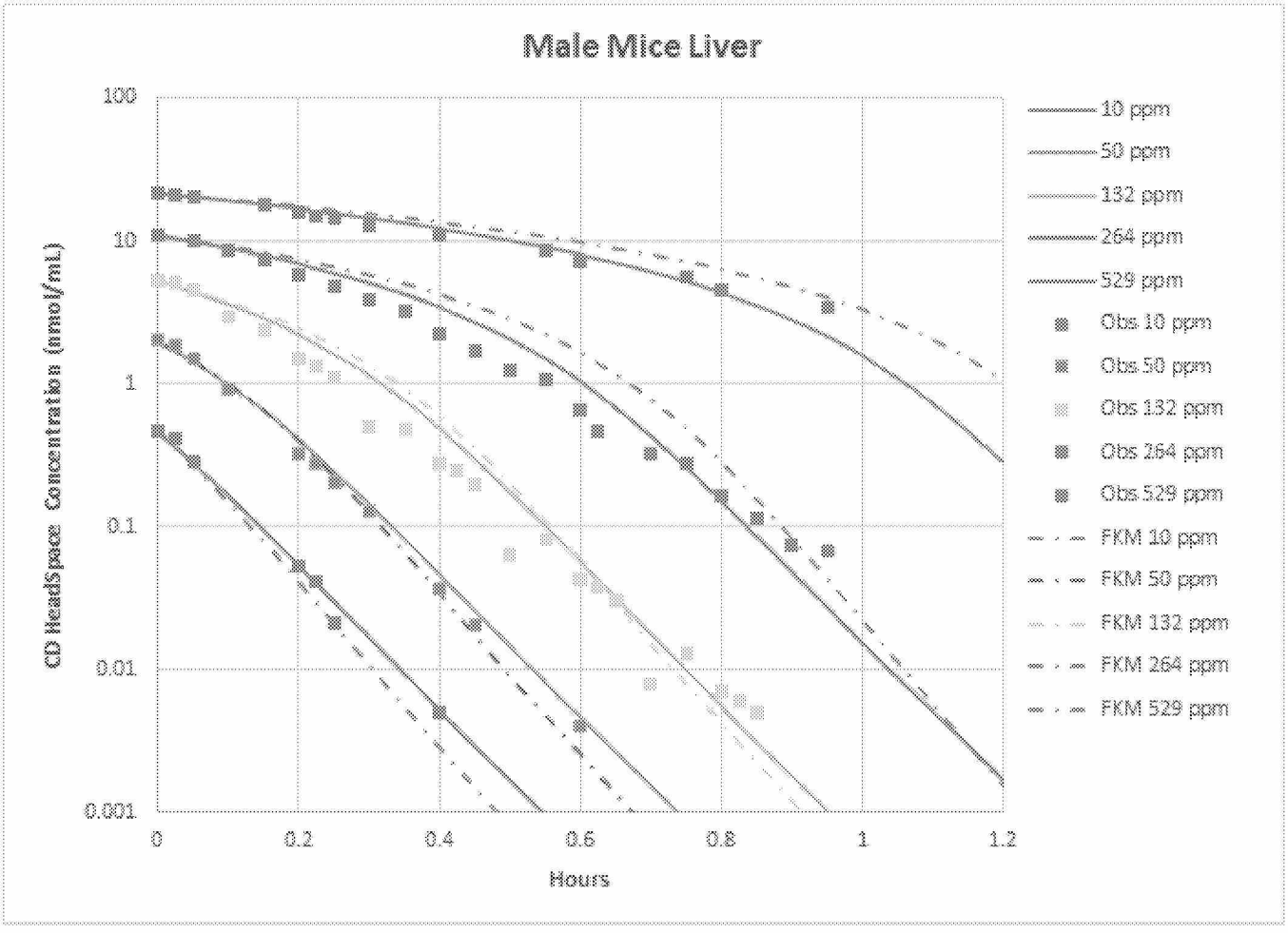
Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/28/2018 8:50:10 PM
To: Jerry Campbell [JCampbell@ramboll.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: RE: Chloroprene In Vitro model

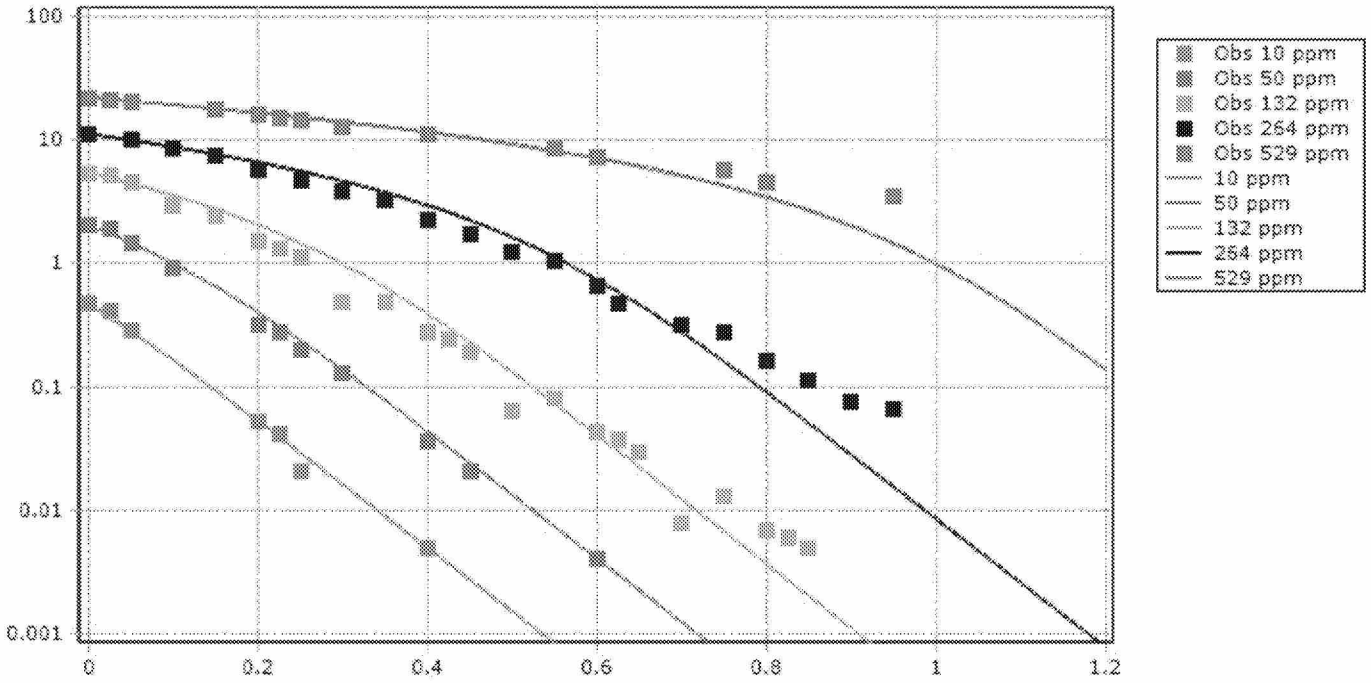
OK, so the first other thing I noticed was that the sampling time (TI) was set to 0.2 h, but clearly samples were taken at a higher frequency. To somewhat quickly get the model to allow for a variation in that, I can't use the procedural, as different sampling intervals changes the length of the output vector, so I can't combine the results in a single array. There's other ways around that, but my cluge was to treat sampling as a continuous loss at rate = VING/TI, where TI is calculated for each data set as TFINAL/NSAMPLE; i.e., the time of the final sample over the number of samples minus the one at time 0.

With the model changed to allow distribution between air and medium (so separate sub-compartments), TI fixed at 0.2 h, but an extremely high mass transfer coefficient (KGL) for air-medium, I get this, compared to the plot (for the Yang parameters) in the spreadsheet that Jerry sent (keep scrolling down):





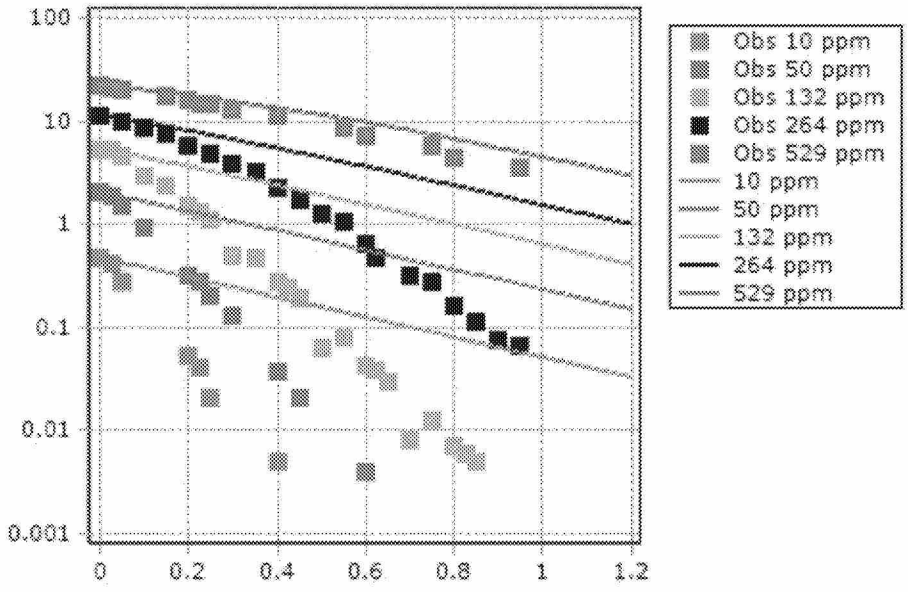
I'd say that's pretty good reproduction! Now, using the variable sampling time (TI), as described above:



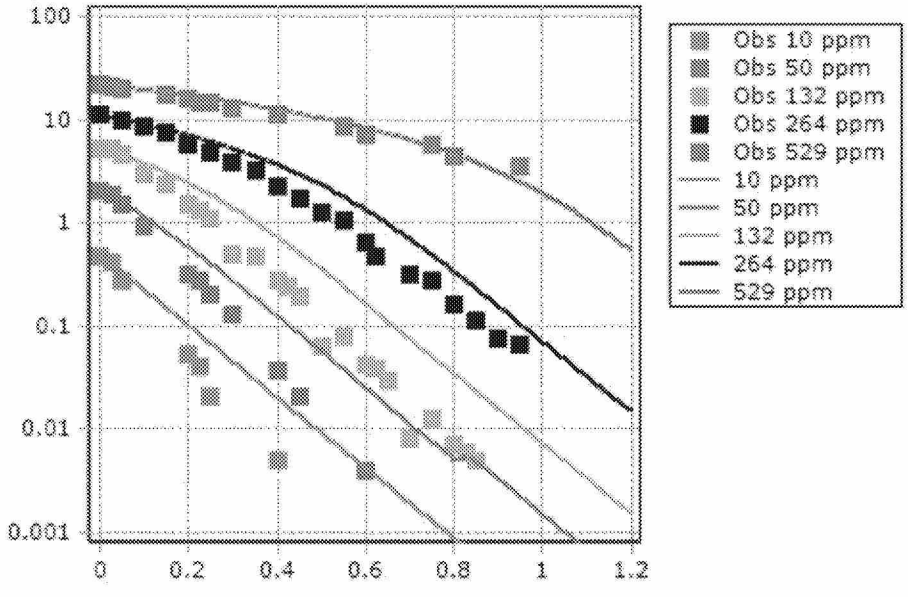
The difference isn't huge, but it's a difference…. For many of the experiments the interval is a fixed 0.2 h, but the male rat and mouse lung, and male rat lung are much more frequent. For the male mouse lung the metabolism is slower, which means the relative impact of this term will be greater.

Ideally the actual sample times should be used, with the scheduled procedural. That's a bit more programming but not terribly difficult. One will just need to deal with the fact that the output from each simulation will be a vector of a different length.

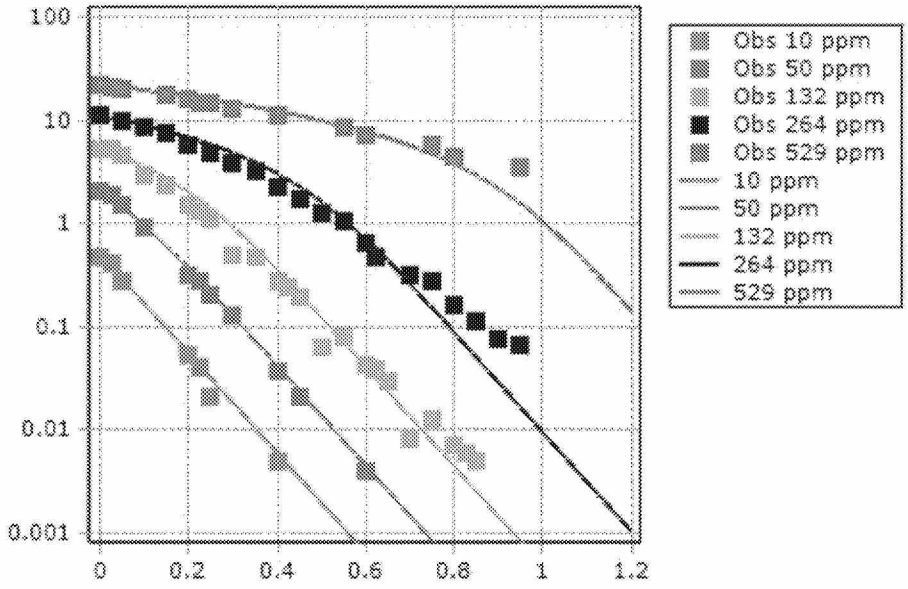
The bigger thing is the gas phase mass transfer. From my '93 benzene paper, the kg = 0.434 ml/min * 60 min/h * 0.001 L/ml = 0.026 L/h. Using that constant, so rate of movement from air to liquid (net) = 0.026*(Ca1 – Cm1/P1), I get:



Really bad, but then there may have been much less mixing in my smaller vials than Matt's, so I increased KGL by 10x, to 0.26:



I then reduced the Km from 1.36 to 0.8 (a bit of trial and error):



Based on this, I'd say that there's a very good chance that the gas-liquid mass transfer is a significant factor, and is likely to impact the estimation of Km (perhaps the goodness of fit of the fixed-Km model). The difficulty is that we need control incubation data to determine the correct value of KGL.

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, August 28, 2018 11:07 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Yes, it should be +ARLOSS. I must have hit the wrong key yesterday when I noticed it was missing from the equation.

Jerry Campbell
Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, August 28, 2018 8:42 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Thanks, Jerry. I've forwarded to Alan who is getting back to his evaluation of the primary model. I'm hoping we can get through the model code evaluation by the end of next week…

Well, I just looked at the .csl and see this:

```
!MASS BALANCE
  CHECK1 = A10 - (A1+A1M+A1I+ ARLUNGVK-ARLOSS)
```

But that should be +ARLOSS?

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 27, 2018 4:30 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: Chloroprene In Vitro model

Paul,

I've uploaded a zip folder (INVITROMODEL AND GRAPHS.zip) with the full workspace for the in vitro model and Excel files with the figures. There is a spreadsheet with a list of the m-files and a short description. Let us know if something doesn't work or you have any questions.

Jerry Campbell

Managing Consultant

D 919-765-8022
jcampbell@ramboll.com

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USA
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Message

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To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]; HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]; Jerry Campbell [JCampbell@ramboll.com]
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Subject: RE: Chloroprene In Vitro model
Attachments: chloroprene in vivo study.doc

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Subject: RE: Chloroprene In Vitro model

Paul,

Harvey is correct. 2004b is closed chamber work.

Matt

Matthew Himmelstein
DuPont Haskell Global Centers
Phone 302 451 4537

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Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Hi Paul

When you talk about the nose-only in vivo PK data from 2004, were you referring to the closed chamber studies that Marina Evans and Elaina Kenyon performed for the Himmelstein et al. 2004b publication?

Harvey Clewell
Principal Consultant

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hclewell@ramboll.com

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Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
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If data are obtained (from archives or newly developed) that show that mass transfer is a factor, it will then be up to Denka/Ramboll to revise the in vitro parameter estimation accordingly, and propagate that into the in vivo model, before we would continue our QA.

As indicated in previous emails, our QA will also involve comparing model predictions to the nose-only in vivo PK data from 2004: the model should be able to fit with parameters adjusted in a way consistent with the hypothesis that there may be an effect of the exposure system on respiration, but this would not be exposure-concentration-dependent. That will require creating model scripts to run these simulations and compare model outputs to the data. While we are

prepared to do that work as part of our QA, provided that the mass transfer data become available, we are not planning to begin that work until those data are available and any necessary revisions of the in vitro modeling have been completed. Alternately, Ramboll colleagues could create the scripts in the meantime, which would speed up the QA.

Sincerely,
-Paul

~~~~~~~~~~~~~~~~~~~~~~

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Sent: Wednesday, September 05, 2018 12:06 PM
To: 'HIMMELSTEIN, MATTHEW W' <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Sorry. I was also wondering at the volume being 1.6 mL bigger than advertised, it seemed like a large discrepancy.

A memo is attached, but here is what I've gotten from looking at the code in the appendix of the report you sent:

- Data to indicate that mass transfer resistance is not significant are still lacking.
- The sample volume (VINJ) for all the CP ***oxidation*** experiments in the 2004 paper should be ~ 400 uL, including male mouse and rat liver and lung data. But the code in the report uses 385.8 uL for male data and exactly 200 uL for male data. Is the higher accuracy for the rodent male and human data supported by some measurements?
- Assuming a similar accuracy, the vial volume (VVIAL) for all experiments described in the 2004 paper should be 0.0120 L. This value should be used for male mouse and rat liver and lung data. (We'll use 0.0116 L for the female mouse and rat data and the kidney data.)

Thanks,
-Paul
~~~~~~~~~~~~~~~~~~~~~~

Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

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Incorporation of *in vitro* metabolism data and physiologically based pharmacokinetic modeling in a risk assessment for chloroprene

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Commented [HC1]: Check whether it's OK to invite Matt to be an author.

Commented [HC2]: Ask Miyoung what address to use.

Commented [HC3]: Ask Mel and Darol if they're OK with using Hamner as their affiliation

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Abstract

Physiologically based pharmacokinetic (PBPK) modeling has now been applied in risk assessments for a variety of environmental chemicals by regulatory agencies worldwide. However, the development of these models has typically required the use of *in vivo* experimental animal or human data to estimate key parameters such as uptake, metabolism and elimination. Some agencies also require the use of separate *in vivo* data to demonstrate the validity of the model. As toxicology and risk assessment move forward in the 21st century, requirements for conducting *in vivo* studies will increasingly limit the application of PBPK modeling. We have developed a PBPK model for chloroprene in the mouse, rat and human that relies solely on *in vitro* data. The predictions of the model were consistent with pharmacokinetic data from a 6-hr, nose-only chloroprene inhalation study that we conducted with female B6C3F1 mice, the most sensitive species/gender for lung tumors in the 2-year bioassays conducted with chloroprene. We have applied the PBPK model in a risk assessment for chloroprene using *in vitro* data on metabolism in the lung target tissue in the mouse and human; inhalation cancer risk estimates obtained with the PBPK model are lower than the current estimates in IRIS by more than an order of magnitude. Given the potentially high impact of species differences in pharmacokinetics on estimates of human risk, the added value of *in vivo* data, particularly human data, should be evaluated on a case-by-case basis before requiring it for acceptance of a PBPK model for such applications.

Key Words: chloroprene, inhalation, PBPK, cancer risk assessment

Introduction

Chloroprene (CAS # 126-99-8) is a highly volatile chlorinated analog to 1,3-butadiene that is used in the manufacture of polychloroprene rubber (Neoprene). A cancer risk assessment for chloroprene conducted by the USEPA (2010) calculated an inhalation unit risk (IUR) of $5x10^{-4}$ per $\mu g/m^3$ based on tumor incidence data from female mice exposed to chloroprene for 2 years (NTP, 1998; Melnick et al., 1999). The USEPA (2010) assessment used a default cross-species extrapolation approach based on chloroprene exposure concentration, despite strong evidence of quantitative differences in chloroprene metabolism in mice and humans that would have a significant impact on the calculated risk (Himmelstein et al. 2004a,b). The metabolism of chloroprene results in the formation of two epoxides that are considered to be responsible for its carcinogenicity (USEPA 2010).

To determine the potential impact of species-specific differences in the production of these epoxides, a physiologically based pharmacokinetic (PBPK) model was developed in a collaborative research effort between DuPont Haskell Laboratory and the USEPA National Health and Environmental Effects Research Laboratory (NHEERL). *In vitro* measurements of partition coefficients and metabolism parameters for chloroprene in mice, rats, hamsters and humans (Himmelstein et al. 2004a) were used in the PBPK model (Himmelstein et al. 2004b) to predict species-specific dose metrics for the production of epoxides in the lung, the most sensitive tissue in the mouse bioassay. The dose metric chosen for this comparison is consistent with the dose metrics used in previous PBPK-based risk assessments for methylene chloride and butadiene, which are also metabolized to reactive metabolites that are considered to be responsible for the observed carcinogenicity. Closed-chamber exposures of mice, rats and hamsters were used to validate the PBPK model's ability to predict the pharmacokinetic behavior of chloroprene *in vivo*. The USEPA (2010), however, did not make use of the PBPK model from Himmelstein et al. (2004b) in their risk assessment, citing the lack of blood or tissue time course concentration data for model validation and indicating that they did not consider the comparisons of model predictions with the closed-chamber studies to be adequate because the data were limited to chloroprene vapor uptake from the closed chambers.

After the time of the USEPA (2010) evaluation, additional metabolism data was published to refine the PBPK model of Himmelstein et al. (2004b). To supplement the data in Himmelstein et

al.(2004a) on liver and lung metabolism in male mouse, male rat, and pooled human cells, Yang et al. (2012) measured liver and lung metabolism in female mouse and female rat, as well as kidney metabolism in male and female mouse, male and female rat, and pooled human cells. The totality of the data from the Himmelstein et al. (2004a) and Yang et al. (2012) *in vitro* metabolism studies was then used to refine the metabolism parameter estimates for the chloroprene PBPK model using Markov-chain Monte Carlo analysis. A comparison of lung dose metric estimates in mouse, rat and human was then performed using the updated metabolism parameters (Yang et al. 2012). These dose metrics were subsequently used in a study comparing genomic responses to chloroprene in the mouse and rat lung (Thomas et al. 2013) and a study comparing human risk estimates derived from mouse bioassay and human epidemiological data (Allen et al. 2014), but to date no *in vivo* blood or tissue time course concentration data has been published with which to evaluate the ability of the chloroprene PBPK model to predict *in vivo* kinetics.

The objectives of the present study were to: 1) Determine the in *vivo* pharmacokinetics of chloroprene via analysis of arterial whole blood concentrations in female B6C3F1 mice during and following a single 6-hour nose-only inhalation exposure, and 2) determine respiratory parameters (breathing frequency and tidal volume) associated with acute chloroprene exposure. In this paper we will demonstrate the ability of the revised chloroprene PBPK model to reproduce the new *in vivo* validation data and will apply the PBPK model in an inhalation cancer risk assessment that properly considers species differences in pharmacokinetics, which is identified as the preferred approach in USEPA's (2005) cancer risk assessment guidance.

Materials and Methods

Test Substance

Exposure atmospheres were generated by metering saturated chloroprene vapor (CAS # 126-99-8) from a stainless-steel pressure vessel reservoir (McMaster Carr, Atlanta, GA) into the nose-only exposure chamber air supply. The concentrated chloroprene vapor was metered through a mass flow controller (MKS Instruments Inc., Andover, MA) and mixed with HEPA-filtered air approximately six feet upstream of the nose-only inlet. Chloroprene vapor was introduced counter-current to the dilution air to facilitate mixing of the vapors with the dilution air.

Chloroprene concentrations were monitored on-line using a gas chromatography system with flame ionization detector (GC-FID). Calibration of the GC-FID for chloroprene analysis was conducted through the analysis of a series of calibration standards produced by introducing pure chloroprene into Tedlar bags containing known volumes of nitrogen gas (nitrogen was metered into the bag using a calibrated flow meter).

Test Animals and Housing

Female B6C3F1 were purchased from Charles Rivers Laboratories, Inc (Raleigh, NC) at 8 weeks of age and acclimated to their surroundings for approximately two weeks prior to use. Following acclimation animals were assigned to a dosing group by randomization of body weights using Provantis NT 2000, assigned unique identification numbers, cage cards, and housed (1/cage) in polycarbonate cages with standard cellulose bedding. Animals were housed in a humidity and temperature controlled, HEPA-filtered, mass air-displacement room provided by the AAALAC accredited animal facility at The Hamner. This room was maintained on a 12 hour light-dark cycle at approximately 64oC-79oF with a relative humidity of approximately 30-70% (Room monitoring data available upon request). Rodent diet NIH-07 (Zeigler Brother, Gardners, PA) and reverse osmosis water was provided ad libitum except during exposures. Food and water was withheld from all animals during the chloroprene exposures. Prior to the start of the chloroprene exposure, animals were weighed and their weights were recorded.

The Hamner Institutes for Health Sciences was fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). Currently acceptable practices of good animal husbandry were followed per National Research Council's Guide for the Care and Use of Laboratory Animals (NRC, 1996) and were in compliance with all appropriate parts of the Animal Welfare Act (1966). In addition, the study design and protocol were approved by The Hamner Institutes' Institutional Animal Care and Use Committee (IACUC) prior to the initiation of study.

Inhalation Exposures

Inhalation exposures were conducted at 13, 32, and 90 ppm for 6 hours. Arterial blood was collected at a total of 6 time-points, 0.5, 3, and 6 hours during exposure and 5, 10, and 15 minutes post-exposure. To support collection of whole blood during the exposures, nose only

towers were fitted with specially designed nose only exposure tubes. These exposure tubes were manufactured from 50 mL polypropylene bulb irrigation syringes (Sherwood Medical, St. Louis, MO). Three elongated holes (0.625" x 1.125") were drilled into the wall of the syringe to allow access to the thorax of the mouse during chloroprene exposure. A second irrigation syringe was cut to form a sleeve around the first syringe to provide an air tight barrier during the exposures. This sleeve was pulled back during the exposure to allow for the injection of pentobarbital (100 mg/kg) while the animal continued to inhale chloroprene. Arterial blood was removed directly from the mouse via cardiac puncture while the mouse was still housed in the syringe and breathing chloroprene. During collection of blood samples, small amounts of air (0.1 to 1 mL) collected in some of the sampling syringes. Tests were conducted to determine if the presence of this air during sampling would impact the final chloroprene concentrations.

Plethysmography

A total of 16 mice (4 per exposure group including air controls) were used for the purpose of collecting tidal volume and breathing frequency. Data were acquired using modified nose-only Buxco plethysmograph tubes for pulmonary function monitoring. Data from control mice were collected prior to the first chloroprene exposure. Plethysmography data from both control and exposed mice were collected for 2-3 hours.

Blood Sampling

Collection of whole blood from Chloroprene exposed mice was conducted using nose only towers and specially designed nose only exposure tubes. Whole blood was collected at 0.5, 3, and 6 hours during exposure and 5, 10, and 15 minutes post-exposure. Whole blood collection during chloroprene exposures (0.5, 3, and 6 hour time points) were done using the specially designed nose only exposure tubes mentioned in sections 3.2.1 and 3.2.2 above.

Blood Analysis

Quantification of Chloroprene in whole blood was conducted by headspace sampling with analysis by gas chromatography mass spectrometry (GC/MS). The sampling method to be used, headspace analysis, as well as the GC/MS method were based on the previously published method for the analysis of 1,3-butadiene in whole blood from mice and rats (.

Briefly, 200 µL of whole blood, obtained by cardiac puncture, was transferred into pre-labeled, capped, and weighed airtight headspace vials (1.5 mL autosampler vial). Sample vials were weighed to obtain an accurate estimate of sample size and allowed to equilibrate at room temperature for 2 hours. Once equilibration was complete, samples were analyzed using an Agilent 5973 mass spectrometer coupled to an Agilent 6890 gas chromatograph. The mass spectrum was run in electron impact mode with selective ion monitoring (instrumental conditions are listed below).

Calibration curves were prepared by spiking stock control whole blood with known amounts of chloroprene obtained as a certified standard solution of chloroprene in methanol (see materials section 2.3 above). Quality control samples were prepared by spiking control rat plasma with a certified CD standard (see below). QC samples were spiked to low (near the first calibration point), medium (near the middle of the calibration curve), and high (near the highest point of the calibration curve) levels. Aliquots of the prepared QC's were placed in sealed GC vials (3 aliquots for each level, 9 total) and frozen at -80 °C until required (GC vials had a minimum of headspace prior to freezing). On the blood collection days, a low-, middle-, and high-level QC was thawed and allowed to come to room temperature for 4 hours. After this time, the QC samples were "sampled" with a syringe identical to those being used for the collection of whole blood, placed in a GC vial in a manner identical to that of the whole blood collection, and analyzed along with the samples and standards.

Chloroprene PBPK Model

The structure of the PBPK model used in this study (Figure 1) is based on the PBPK model of chloroprene described in Himmelstein et al. (2004b), as modified by Yang et al. (2012). As in previous models of volatile organic compounds (Ramsey and Andersen, 1984), the blood is described using a steady-state approximation and the model assumes blood-flow limited transport to tissues and venous equilibration of tissues with the blood. Metabolism is described in the liver, lung and kidney using Michaelis-Menten saturable kinetics. It has been converted from ACSL, a continuous simulation language, to R, an open source programming language, to improve its portability. The R code for the model is included at the end of the Supplemental Materials.

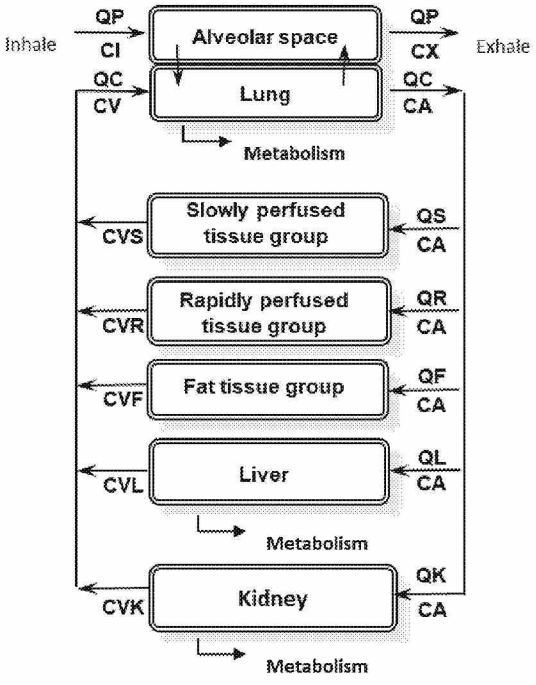

Figure 1: Choroprene PBPK model diagram.

Commented [HC4]: Define parameter abbreviations.

All physiological parameters in the model for mouse, rat and human (Table S-1 in the Supplemental Materials) are taken from Brown et al. (1997) except for the cardiac output in the mouse and the alveolar ventilation and cardiac output in the human. While the alveolar ventilation in the mouse is taken from Brown et al. (1997), relying on the value of cardiac output reported in Brown et al. (1997) would result in a value of 11.7 L/hr/$bw^{3/4}$ for cardiac output (QCC). If used with the Brown et al . (1997) value of 29.1 L/hr/$bw^{3/4}$ for alveolar ventilation

(QPC), this would result in a serious mismatch between ventilation and perfusion (V/Q ratio >> 1). The developers of the PBPK model for methylene chloride (Andersen et al. 1987), argued that it would be more biologically realistic to assume that the V/Q ratio was closer to 1 at rest, and stated that their previous experience with PBPK modeling of data on clearance of chemicals in the mouse under flow-limited metabolism conditions supported the use of a higher value for QCC. Therefore, the value of QCC in the current model was calculated by dividing the alveolar ventilation from Brown et al. (1997) by MCMC estimates of a V/Q ratio for the mouse based on pharmacokinetic data for exposures to another volatile organic chemical, methylene chloride (Marino et al. 2006), which was used in the USEPA (2011) inhalation cancer risk assessment for that chemical. In the case of the human, EPA typically uses a ventilation rate of 20 L/day, reflecting an average activity level, rather than a resting value. Since the values for alveolar ventilation and cardiac output in Brown et al. (1997) are resting values, we used the values calculated for the PBPK model of vinyl chloride (Clewell et al. 2001), which was developed for the USEPA (2000) for their cancer risk assessment for that chemical, and which were therefore calculated to correspond to a total ventilation of approximately 20 L/day.

Apart from the physiological parameters, the model is not based on any *in vivo* data. The partition coefficients (Table S-2 in the Supplemental Materials) were calculated from the results of *in vitro* assay data reported by Himmelstein et al. (2004b). The model parameters for metabolism in the liver, lung and kidney (Table S-3 in the Supplemental Materials) were derived by in vitro to in vivo extrapolation (IVIVE) of the results of the Markov-chain Monte Carlo (MCMC) analysis conducted by Yang et al. (2012) using the *in vitro* metabolism data reported in Brown et al. (2004a) and Yang et al. (2012). The details of the IVIVE calculations are provided in the Supplemental Materials.

To model the experimental data in the mouse nose-only inhalation exposures reported here, only the alveolar ventilation and cardiac output were altered. The average ventilation rate measured in the study was used to calculate an alveolar ventilation for use in the model, assuming 2/3 of total ventilation is alveolar (Brown et al. 1997) and the cardiac output was calculated by dividing the alveolar ventilation by the V/Q ratio from Marino et al. (2006).

The dose metrics calculated in the model represent micromoles of chloroprene metabolized per day per gram lung. This dose metric was chosen because the lung is the tissue with the highest

tumor incidence in the chloroprene inhalation bioassays (NTP, 1998) and the carcinogenicity of chloroprene is believed to result from its metabolism to reactive epoxides (Himmelstein et al. 2004a,b).

Results

Chloroprene Exposure Atmospheres

Chloroprene concentrations were monitored in the nose only chambers during the 13,32, and 90 ppm exposures, as well as in the control nose-only tower. All three target concentrations were well within 10% of their nominal levels.

Plethysmography

Figure 2 shows the measured minute volumes for the three exposure groups and controls. The data is represented as average values (diamonds) with standard deviation error bars. The data is provided in Table S-2 in the Supplemental Materials. There is no evidence of a concentration-related effect of short-term exposure to chloroprene on ventilation in mice. The average ventilation rate across all four exposure groups, including controls, was 56.2 mL/min. The average body weight for the mice in the study was 22g; therefore, this ventilation rate equates to a model parameter for alveolar ventilation (QPC) of 37.6 L/hr/$bw^{3/4}$. The corresponding model value of QCC in this study is obtained by dividing QPC by the V/Q ratio of 1.45 for the mouse (Marino et al. 2006), yielding a value for QCC of 26.0 L/hr/$bw^{3/4}$, which compares well with the QCC of 24.2 estimated for mouse exposures to methylene chloride (Marino et al. 2006).

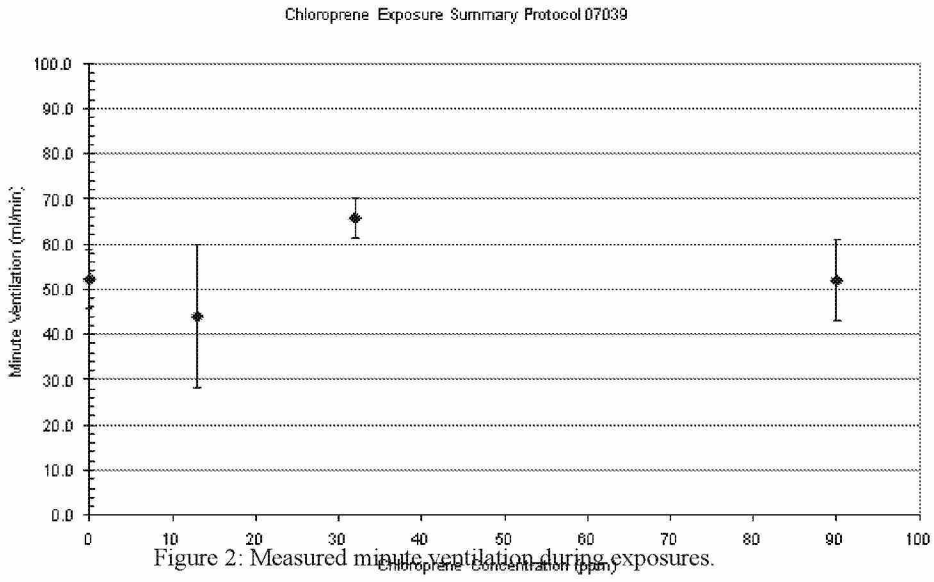

Figure 2: Measured minute ventilation during exposures.

Arterial Blood Chloroprene Concentrations

Figure 3 shows the average CD blood concentrations for all three single day exposures (Data are provided in Table S-3 of the Supplemental Materials). Average blood chloroprene concentrations are represented by the symbols with standard deviations for each treatment group represented with error bars.

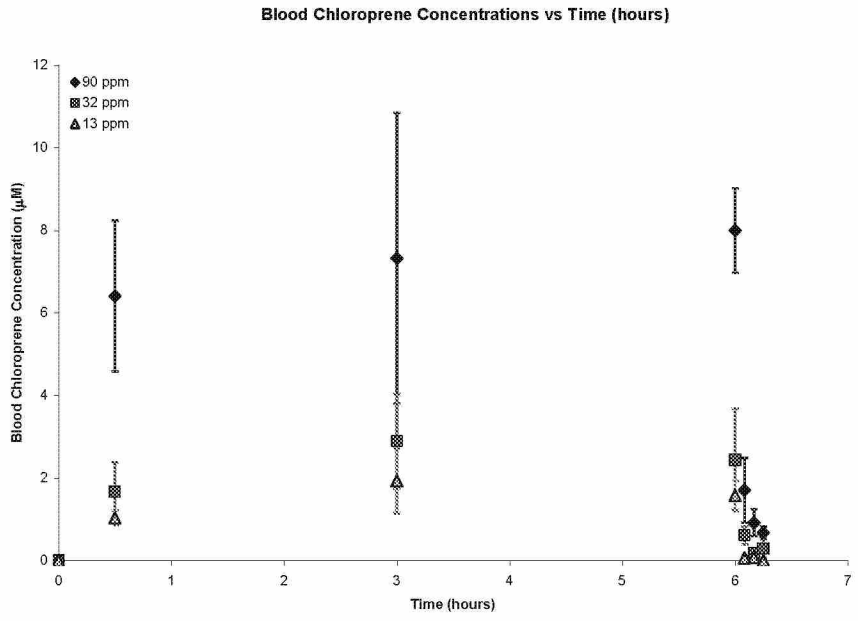

Figure 3. Arterial blood chloroprene concentrations during and following a single nose-only exposure of female B6C3F1 mice to chloroprene at 13, 32 and 90 ppm for 6 hours. Average blood chloroprene concentrations (symbols) and standard deviations (error bars) are shown for each treatment group.

PBPK Modeling of the Nose-Only Inhalation Study

The nose-only study described above was simulated with the chloroprene PBPK model using the parameters in Tables S1, S2, and S3, except for QPC and QCC, where the study-specific values derived from the plethysmography data were used. As shown in Figure 4, using only in vitro-derived parameters the model predictions for arterial blood concentrations during and after the 6-hr chloroprene exposures are in good agreement with the data collected in the study, with model predictions generally lying within roughly a factor of two of the means of the experimental data. No model parameters were adjusted to provide agreement with the new data.

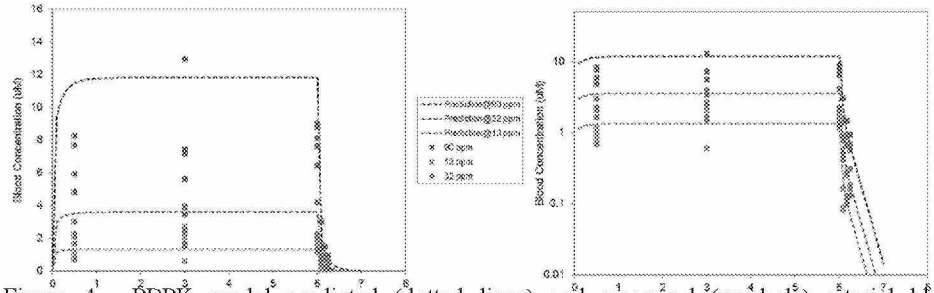

Figure 4. PBPK model predicted (dotted lines) and measured (symbols) arterial blood concentrations during and following 6-hr exposures of B6C3F1 mice to chloroprene at 13, 32 and 90 ppm. The same data and model predictions are shown using a linear y axis (left) and a logarithmic y axis (right). The linear plot provides a better comparison for concentrations, whereas the logarithmic plot provides a clearer comparison for the post-exposure clearance.

PBPK Model Parameter Sensitivity

Parameter sensitivity analysis was conducted with the model under two scenarios: (1) the prediction of blood concentrations in the mouse nose-only study, and (2) the prediction of dose metrics for the mouse bioassay exposures and for the human at 1 ppm continuous exposure. The results are shown in Figures 5 through 7, which display the normalized sensitivity coefficients (fractional change in prediction divided by fractional change in parameter) for parameters with a coefficient greater than 0.1 in absolute magnitude. A positive coefficient indicates the direction of change of the prediction is the same as the direction of change of the parameter. The parameters were changed by 1%, one at a time.

As shown in Figure 5, only 4 model parameters have coefficients greater that 0.1 in absolute magnitude: alveolar ventilation, cardiac output, blood:air partition coefficient and fractional blood flow to liver. All of these parameters were either directly measured or based on data from the literature and can be considered to have low uncertainty. When predicting lung dose metrics in the female mouse (Figure 6), the sensitive parameters include the same parameters as for prediction of blood concentration, plus the parameters for lung metabolism and the body weight. The sensitive parameters for predictions of lung dose metrics in the human (Figure 7) are similar

to those in the mouse, except that a single clearance parameter is used in the human due to the low rate of metabolism in the human lung.

Commented [HC5]: Decide whether to use saturable lung clearance in human.

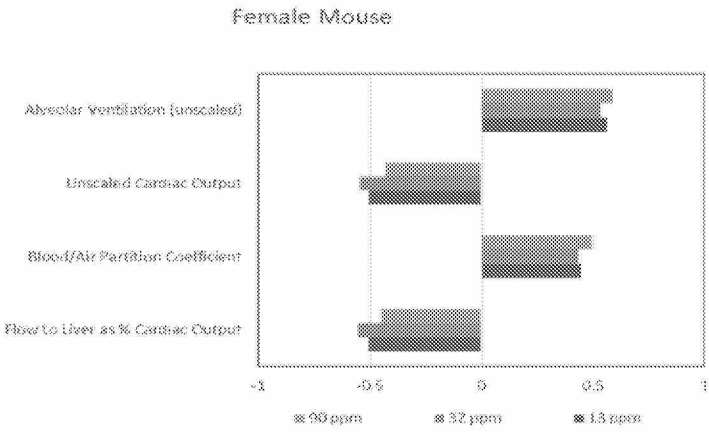

Figure 5. Parameter sensitivity coefficients for the chloroprene PBPK model for the prediction of arterial blood concentrations in the nose-only study.

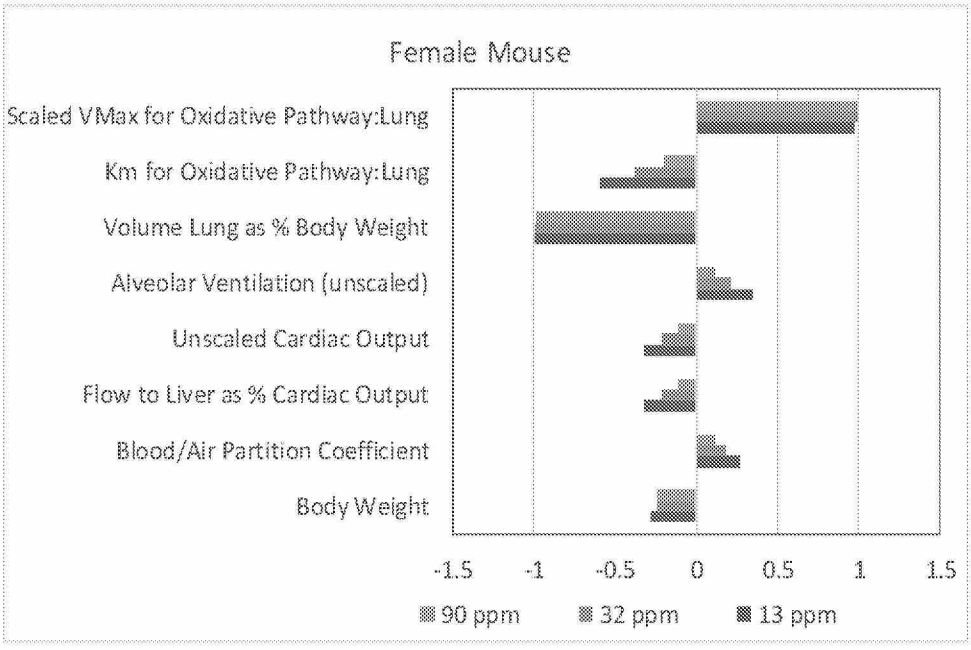

Figure 6. Parameter sensitivity coefficients for the chloroprene PBPK model for the prediction of lung dose metrics in the female mouse for exposures in the 2-year bioassay.

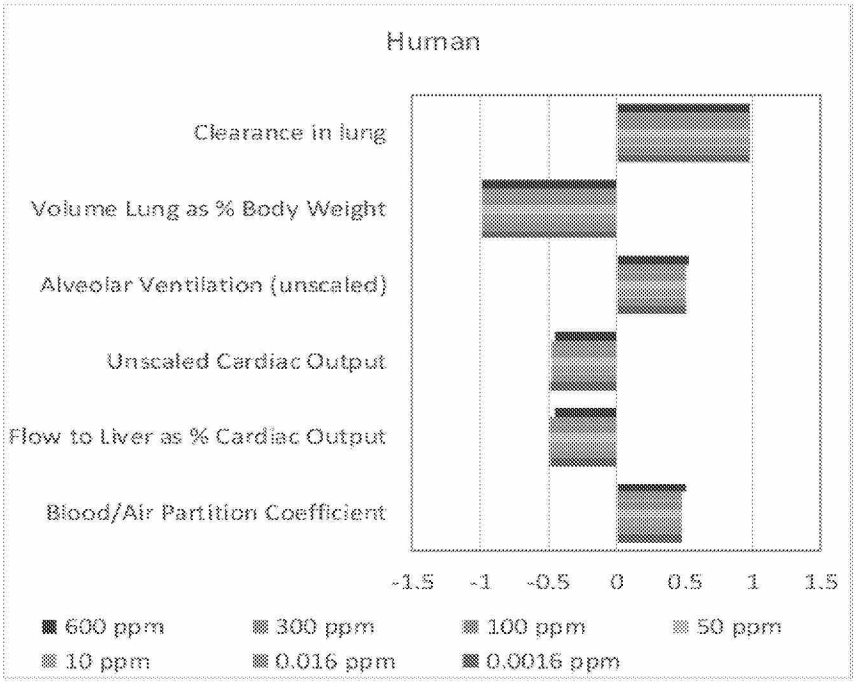

Figure 7. Parameter sensitivity coefficients for the chloroprene PBPK model for the prediction of lung dose metrics in the human for continuous exposure at 1 ppm.

Discussion

In this study we have characterized the in *vivo* pharmacokinetics of chloroprene in female B6C3F1 mice during and following a single 6-hour nose-only inhalation exposure over a range of concentrations encompassing those used in the NTP (1998) bioassays. The date we report on arterial whole blood concentrations and respiratory parameters (breathing frequency and tidal volume) during and after these exposures provide a solid basis for evaluating the ability of the chloroprene PBPK model to predict internal exposure in the bioassays. We have also demonstrated the ability of a revised chloroprene PBPK model to reproduce the new *in vivo* data and have applied the PBPK model in an inhalation cancer risk assessment that incorporates species differences in pharmacokinetics. The IUR obtained with the PBPK model is more than an order of magnitude lower that IUR published by EPA (2010), which was based on inhaled chloroprene concentration.

Acknowledgments

From the Hamner Institutes: Dr. Mark A. Sochaski (analytical chemistry), Carl U. Parkinson, Jr. (inhalation generation/characterization), Paul W. Ross, Carol M. Bobbitt and Kathy A. Bragg (animal care). The authors would also like to thank Paul Schlosser, EPA/NCEA, for his helpful comments and suggestions on an early version of this manuscript. This research was supported by SEHSC (*in vivo* study) and Denka Performance Elastomer, LLC (PBPK modeling).

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Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/28/2018 3:57:31 PM
To: Jerry Campbell [JCampbell@ramboll.com]
CC: Harvey Clewell [HClewell@ramboll.com]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: RE: Chloroprene In Vitro model

P.S. This is from the benzene study. It took about 4 min to reach 40% of initial gas-phase concentration (before back-diffusion became significant). That's almost identical to the initial rates in the CP data.

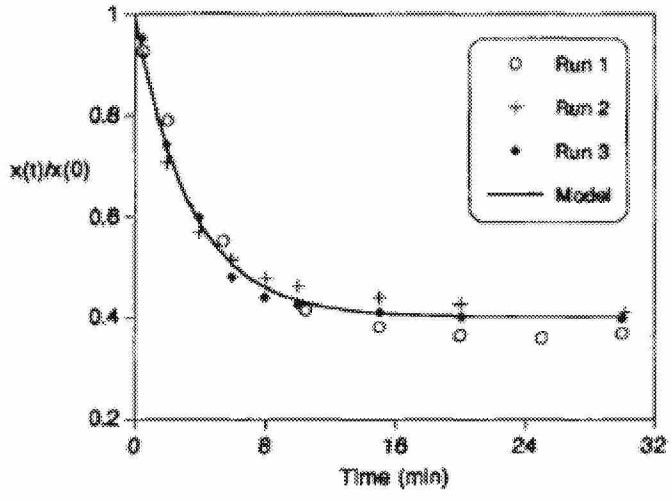


Fig. 3. Partitioning of benzene from liquid phase, into gas phase, in the absence of microsomes under incubation conditions (37°C shaker); $x(t)$ = concentration of benzene in the liquid phase at time = t; $x(0)$ = concentration of benzene in the liquid phase at time = 0. Different initial values, $x(0)$, were used for each run. The model is as depicted in Figure 1 with the rates of biotransformation ($r_1 - r_3$) set to zero.

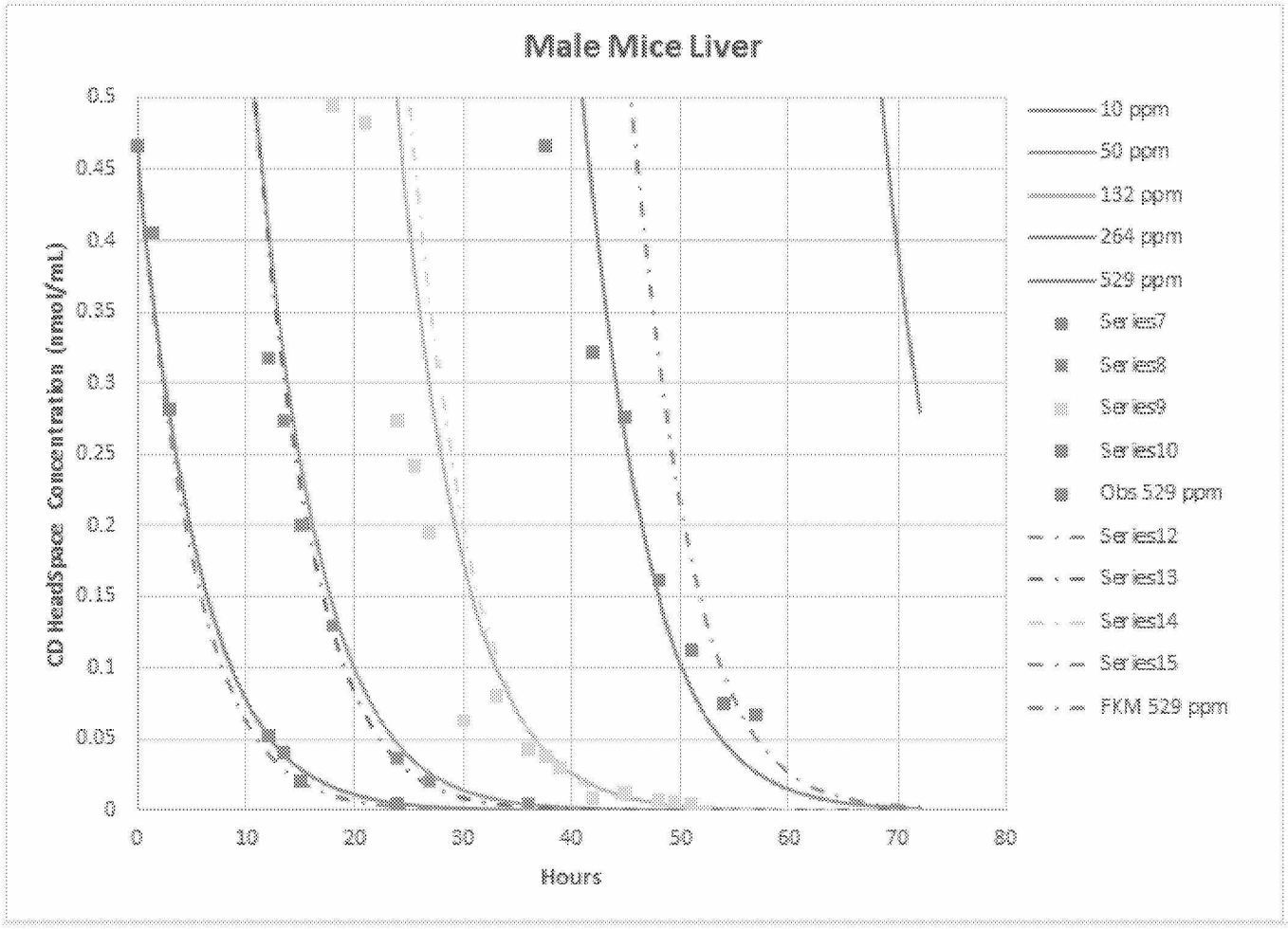
From: Schlosser, Paul
Sent: Tuesday, August 28, 2018 11:47 AM
To: 'Jerry Campbell' <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Luckily just the mass balance check!

I am concerned that the model assumes instantaneous equilibrium between air and medium. When metabolism is slow, that's probably good, but the mouse liver rates are pretty high (at low concentrations). Below is replotted on linear scale vs. time in minutes. The initial decline is very close to what I saw, too many years ago, for the initial rate of air:liquid equilibration of benzene in the absence of microsomes. So these may not be giving an accurate value of Vmax/Km.

Matt used bigger vials than I did (10 ml vs 4 ml), though the same incubation mixture volume (1 ml). But as a test I will use the same mass transfer constant that I got for BZ to see if there's any impact. I'll assume the system is at equilibrium at the start of the incubation, and use the air:water PC for chloroprene. If adding the term doesn't impact the simulations significantly, then OK.

-Paul



From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Tuesday, August 28, 2018 11:07 AM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Yes, it should be +ARLOSS. I must have hit the wrong key yesterday when I noticed it was missing from the equation.

Jerry Campbell
Managing Consultant

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jcampbell@ramboll.com

From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Tuesday, August 28, 2018 8:42 AM
To: Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Thanks, Jerry. I've forwarded to Alan who is getting back to his evaluation of the primary model. I'm hoping we can get through the model code evaluation by the end of next week…

Well, I just looked at the .csl and see this:

!MASS BALANCE
CHECK1 = A10 - (A1+A1M+A1I+ ARLUNGVK-ARLOSS)

But that should be +ARLOSS?

-Paul

From: Jerry Campbell [mailto:JCampbell@ramboll.com]
Sent: Monday, August 27, 2018 4:30 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Harvey Clewell <HClewell@ramboll.com>
Subject: Chloroprene In Vitro model

Paul,

I've uploaded a zip folder (INVITROMODEL AND GRAPHS.zip) with the full workspace for the in vitro model and Excel files with the figures. There is a spreadsheet with a list of the m-files and a short description. Let us know if something doesn't work or you have any questions.

Jerry Campbell

Managing Consultant

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Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/6/2018 12:49:03 PM
To: AFranzen@ramboll.com
Subject: RE: Allison Franzen shared the folder "Chloroprene PBPK Model" with you.

Alsion,

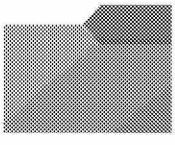
I've received and downloaded this, but the model folder contains none of the scripts listed in the documentation spreadsheet.

-Paul

From: Allison Franzen [mailto:no-reply@sharepointonline.com]
Sent: Friday, August 03, 2018 1:40 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Allison Franzen <AFranzen@ramboll.com>
Subject: Allison Franzen shared the folder "Chloroprene PBPK Model" with you.

This folder contains the documentation and workspace for the R version of the Chloroprene PBPK model.

This link only works for the direct recipients of this message.



Chloroprene PBPK Model

Open

Microsoft OneDrive

Microsoft respects your privacy. To learn more, please read our Privacy Statement.
Microsoft Corporation, One Microsoft Way, Redmond, WA 98052

Message

From: Harvey Clewell [HClewell@ramboll.com]
Sent: 8/3/2018 6:02:25 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]
CC: Robinan Gentry [rgentry@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Allison Franzen [AFranzen@ramboll.com]; Jerry Campbell [JCampbell@ramboll.com]; Miyoung Yoon [myoon@toxstrategies.com]; Sonja Sax [SSax@ramboll.com]
Subject: transmission of PBPK model for chloroprene

Hi Paul

As promised, we are providing you with the PBPK model for chloroprene written in R, with all the associated scripts and documentation. You should have received a separate email with an invitation to access the files on Microsoft OneDrive. Please let me if you have any problem downloading or opening them. Jerry Campbell would be happy to come over to EPA to help you set up the run environment in R studio and answer any questions you may have about running the model.

I'm looking forward to talking with you about the model and discussing any questions, suggestions, or concerns regarding it. Would it be possible to arrange an initial meeting sometime in the next few weeks. Miyoung Yoon is completing her review of the metabolism parameter scaling approach and I would like to be able to include you in the discussion of her recommendations.

Harvey Clewell

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Message

From: Harvey Clewell [HClewell@ramboll.com]
Sent: 9/20/2018 3:43:28 PM
To: Schlosser, Paul [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=121cf759d94e4f08afde0ceb646e711b-Schlosser, Paul]
CC: HIMMELSTEIN, MATTHEW W [Matthew.W.Himmelstein@dupont.com]; Jerry Campbell [JCampbell@ramboll.com]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]
Subject: Re: Chloroprene In Vitro model

Hi Paul

I don't know why being in the closed chamber effects the ventilation rate in mice either. Jerry suggested it might be related to the efficiency of scrubbing of CO2 and H2O. At any rate, as mentioned in Brown et al., the lower ventilation rate for mice in the closed chamber has been reported in many studies over the years and is not limited to the chloroprene studies at NHEERL. Maybe you should talk with Elaina.

With kind regards,

Harvey Clewell

On Sep 20, 2018, at 8:12 AM, Schlosser, Paul <Schlosser.Paul@epa.gov> wrote:

> Matt,
>
> I saw the other note too, thanks.
>
> The plots are classic for closed chamber, so my goof, but the discussion of how the exposure system might effect respiration had me thinking of nose-only. It doesn't make as much sense to me that the animals would breath differently in a closed vs open chamber.
>
> -Paul
>
> ---
>
> **From:** HIMMELSTEIN, MATTHEW W [mailto:Matthew.W.Himmelstein@dupont.com]
> **Sent:** Thursday, September 20, 2018 8:00 AM
> **To:** Harvey Clewell <HClewell@ramboll.com>; Schlosser, Paul <Schlosser.Paul@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
> **Cc:** Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
> **Subject:** RE: Chloroprene In Vitro model
>
> Paul,
>
> Harvey is correct. 2004b is closed chamber work.
>
> Matt
>
> Matthew Himmelstein
> DuPont Haskell Global Centers
> Phone 302 451 4537

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Wednesday, September 19, 2018 4:41 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>; HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: [EXTERNAL] RE: Chloroprene In Vitro model

Hi Paul

When you talk about the nose-only in vivo PK data from 2004, were you referring to the closed chamber studies that Marina Evans and Elaina Kenyon performed for the Himmelstein et al. 2004b publication?

Harvey Clewell
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From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Wednesday, September 19, 2018 1:39 PM
To: HIMMELSTEIN, MATTHEW W <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <jcampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt, all,

I'm following up to see how things stand regarding the search for additional data. In a separate note Harvey said there should be a report (IISRP?) for the earlier in vitro studies, which it could help to have. Please send any that you have.

As it stands, we have mostly halted our QA review, as it strongly hinges on the equilibration assumption in the in vitro modeling. The code for the in vitro and in vivo models has checked out, issues resolved, and I think all other parameter discrepancies have been resolved -- a few changes but none that should make a really large difference.

I realize it might take some time for files to be retrieved from archives and reviewed, but it's now been a couple of weeks since I provided the written details on what we are seeking. Can you tell us where things stand on your end?

The simulations I've run/provided show that the fits to the low concentration in vitro data depend significantly on the assumption that gas-liquid equilibration is not rate limiting, and the data are consistent with the possibility that it is a factor, requiring a fairly large revision in the estimated Km value(s). As is, my conclusion is that there is uncertainty due to the lack of data on the mass transfer rate, and there isn't an easy way that I can think of (or that we are likely to undertake ourselves) for estimating or bounding that uncertainty. The model results are too uncertain to use, given the data and assumptions.

If data are obtained (from archives or newly developed) that show that mass transfer is a factor, it will then be up to Denka/Ramboll to revise the in vitro parameter estimation accordingly, and propagate that into the in vivo model, before we would continue our QA.

As indicated in previous emails, our QA will also involve comparing model predictions to the nose-only in vivo PK data from 2004: the model should be able to fit with parameters adjusted in a way consistent with the hypothesis that there may be an effect of the exposure system on respiration, but this would not be exposure-concentration-dependent. That will require creating model scripts to run these simulations and compare model outputs to the data. While we are prepared to do that work as part of our QA, provided that the mass transfer data become available, we are not planning to begin that work until those data are available and any necessary revisions of the in vitro modeling have been completed. Alternately, Ramboll colleagues could create the scripts in the meantime, which would speed up the QA.

Sincerely,
-Paul

~~~~~~~~~~~~~~~~~~~~~~~~
Paul M. Schlosser
NCEA, U.S. EPA
M.D. B243-01
RTP, NC 27711
T: 919-541-4130
F: 919-685-3330
E: schlosser.paul@epa.gov

From: Schlosser, Paul
Sent: Wednesday, September 05, 2018 12:06 PM
To: 'HIMMELSTEIN, MATTHEW W' <Matthew.W.Himmelstein@dupont.com>; Jerry Campbell <JCampbell@ramboll.com>
Cc: Harvey Clewell <HClewell@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: Chloroprene In Vitro model

Matt,

Sorry. I was also wondering at the volume being 1.6 mL bigger than advertised, it seemed like a large discrepancy.

A memo is attached, but here is what I've gotten from looking at the code in the appendix of the report you sent:

- Data to indicate that mass transfer resistance is not significant are still lacking.
- The sample volume (VINJ) for all the CP ***oxidation*** experiments in the 2004 paper should be ~ 400 uL, including male mouse and rat liver and lung data. But the code in the report uses 385.8 uL for male data and exactly 200 uL for male data. Is the higher accuracy for the rodent male and human data supported by some measurements?
~~~~~~~~~~~~~~~~~~~~~~~~

- Assuming a similar accuracy, the vial volume (VVIAL) for all experiments described in the 2004 paper should be 0.0120 L. This value should be used for male mouse and rat liver and lung data. (We'll use 0.0116 L for the female mouse and rat data and the kidney data.)

Thanks,
-Paul

Message

From: Schlosser, Paul [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=121CF759D94E4F08AFDE0CEB646E711B-SCHLOSSER, PAUL]
Sent: 8/22/2018 9:32:50 PM
To: Harvey Clewell [HClewell@ramboll.com]
CC: Robinan Gentry [rgentry@ramboll.com]; Allison Franzen [AFranzen@ramboll.com]; Miyoung Yoon [myoon@toxstrategies.com]; Sonja Sax [SSax@ramboll.com]; cvanlandingham@ramboll.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usereda39e51]; Davis, Allen [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a8ecee8c29c54092b969e9547ea72596-Davis, Allen]; Sasso, Alan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cb867519abc4dcea88149d12ef3e8e9-Sasso, Alan]; Vandenberg, John [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dcae2b98a04540fb8d099f9d4dead690-Vandenberg, John]; Thayer, Kris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3ce4ae3f107749c6815f243260df98c3-Thayer, Kri]; Bahadori, Tina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7da7967dcafb4c5bbc39c666fee31ec3-Bahadori, Tina]; Jerry Campbell [JCampbell@ramboll.com]
Subject: RE: transmission of PBPK model for chloroprene

Thanks. I had seen/checked that it matched the Himmelstein paper. As long as a set of calculations can be tracked to the source, I think it's reasonable to not round part-way through. But if the 'source' for our analysis here is the paper, then better not to use information that is otherwise hidden. I didn't think it would have a big impact, but if you had the original data from which those were calculated, we'd like to capture that too.

Alan is part-way through reviewing the code, had to switch to other tasks. He hasn't found anything significant, which is good.

We will need to have or create scripts to reproduce all plots from Matt's papers, both the in vitro system and the in vivo. If you have a clean code package for the in vitro model, that would help.

The initial choice of parameterization has to be ours. We need to have the model plots vs. data before we make any decisions. The likely path is that we'll develop a document showing the quality of model fit for each option/parameter set available and discussing choices made for modeling of bioassays, including statistical uncertainty associated with using more fitted parameters (degrees of freedom). If there's not one that is clearly superior, or there's disagreement about which is best, that discussion would probably need to be in the context of a public meeting.

-Paul

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Wednesday, August 22, 2018 4:22 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <SSax@ramboll.com>; cvanlandingham@ramboll.com; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Jerry Campbell <JCampbell@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

H Paul

With regard to your question regarding the partition coefficient values used in the model, I believe that the tissue:air partition coefficients in the spreadsheet I sent you before were provided to Yuching Yang by Matt Himmelstein, but you'd have to ask him to be sure. They round off to the same values reported in Himmelstein et al. 2004 (Tox Sci

79:28–37) Table 3. The spreadsheet I've attached here uses the rounded off values that were actually published. I prefer using published values rather than raw calculations. Obviously, the rounding makes very little difference in the resulting tissue:blood partition coefficients for the model.

Please let me know if you have any other questions about the model. I was wondering if Jerry and I could get together with you some time to talk about the options for model parameterization to support a risk assessment.

Harvey Clewell
Principal Consultant

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hclewell@ramboll.com

From: Schlosser, Paul <Schlosser.Paul@epa.gov>
Sent: Tuesday, August 14, 2018 4:14 PM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <afranzen@ramboll.com>; Miyoung Yoon <myoon@toxstrategies.com>; Sonja Sax <ssax@ramboll.com>; Cynthia Van Landingham <cvanlandingham@ramboll.com>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Jerry Campbell <jcampbell@ramboll.com>
Subject: RE: transmission of PBPK model for chloroprene

Harvey,

The QA process essentially has two steps:

1) Determine if we can replicate the original study, using those parameters "as is". What's been provided appears successful in this, though I don't see plots for the in vivo gas uptake data of Himmelstein.
2) QA the model code, parameters, data. In this case there is particular attention on the IVIVE. Is it truly predictive?

A component of (2) is tracing all model parameters back to their original source: the paper where the data was first collected/reported, or to a comprehensive physiological review. We have found this is particularly pesky for allometric coefficients, but other derived quantities can also be very hard to replicate. This is why we suggest (and in our own QA do) embedding calculations in a spreadsheet. The first column(s) are numbers exactly as you find them in the source, then the calculations. You've done this for metabolic constants, but not QPC/QCC.

If a parameter is just a little and the results is that there is only a modest fit in the plot of model simulations vs. data (eg, the Himmelstein gas uptake data are fit almost equally well with corrected parameters), that's fine. We then move ahead with the corrected parameters. The assumption is that had the revised plot been submitted for publication, it would have been accepted.

So for now, we aren't looking to refit parameters. But it would help to have the QPC/QCC solidly connected, calculations checked.

-Paul

From: Harvey Clewell [mailto:HClewell@ramboll.com]
Sent: Tuesday, August 14, 2018 3:49 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Robinan Gentry <rgentry@ramboll.com>; Allison Franzen <AFranzen@ramboll.com>; Miyoung Yoon